

*DE 10126434-A1
2001.05.31 2001-1026434(+2001DE-1026434) (2002.12.05) C07D
335/16, A61K 31/382, C07D 409/04, 409/12, 413/04, 417/12

New tricyclic thiocromenone derivatives as metabotropic glutamate receptor-1 (mGluR1) antagonists useful for treating e.g. hemorrhagic stroke and atherosclerosis, especially pain or neurodegenerative diseases

C2003-05426

Addnl. Data: MEIER H, ALLERHEILIGEN S, GERISCH M, SCHOHE-LOOP R, VOERSTE A, MAULER F, DE VRY J, MUELLER T, MEFHESSEL C

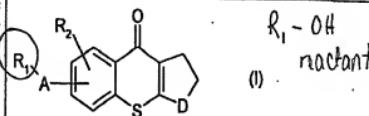
4 NOVELTY

Tricyclic thiocromenone derivatives (I) are new.

5 DETAILED DESCRIPTION

Thiocromenones of formula (I) and their salts, hydrates and/or solvates are new;

B6-B2, 14-A1, 14-A2, 14-C1, 14-E5, 14-E12, 14-F2, 14-F4, 14-F7, 14-F8, 14-F10, 14-G2D, 14-H1, 14-J1A, 14-J1B, 14-J5, 14-J7, 14-L6, 14-M1, 14-N1, 14-N16, 14-S1, 14-S4 .12



R₁ = (i) 6-10C aryl or 5-10 membered heteroaryl (both optionally substituted (os) by one or more of halo, CHO, CONH₂, CN, OH, OCF₃, NO₂, NR₁R₂, tetrazolyl or alkoxy carbonyl; or alkyl, alkoxy, 1-6C acyl or alkylthio (all os by OH, morpholinyl, 1-6C acetoxy or halo); (ii) 3-12 membered carbocycl or 4-2 membered heterocycl (both by one or more of alkyl, alkoxy, 1-6C acyl, alkoxy carbonyl or oxo); or (iii) R₅-E;
A = direct bond, O, S, NR₄, CO, SO, SO₂, SO₂O, CONR₂, SO₂NR₃, OSO₂, NR₂CO, NR₁SO₂, R₁SO₂O, NR₁₂SO₂R₁₃ or

| DE 10126434-A+

NR₁₃CONR₁₅; or R₁A = H or NH₂; R₃, R₄ = H, alkyl or 1-6C acyl;

E = optionally unsaturated 1-10C alkane diyl;
R₅ = H, CONH₂, halo, OH, NO₂, CF₃, NH₂, mono- or dialkylamino, alkoxy, 6-10C aryl, 5-10 membered heteroaryl or 4-10 membered heterocycl (by oxo and/or alkyl and optionally fused benzene), where aryl, heteroaryl and benzo groups are os by halo, CN, CF₃, OCF₃, NO₂ or alkyl;

R₆-R₁₃ = 3-8C cycloalkyl or optionally unsaturated alkyl (os by OH, phenyl (os by halo or 1-4C alkyl), alkoxy, alkoxy carbonyl or cycloalkyl);

R₈, R₉, R₁₀, R₁₁, R₁₂ = H;

R₂ = H, halo, or alkyl or alkoxy (both os by 1 or 2 of OH, alkoxy or mono- or dialkylamino);

D = 3-10C hydrocarbylene (os by F).

Alkyl moieties have 1-6C unless specified otherwise.

Provided that:

(1) the R₁-A group is in the 2- or 3-position of the thiocromenone ring; and

(2) the compound 2-chloro-6,7,8,9,10,10A-hexahydro-cyclohepta(b)thiocromen-11(5H)-one is excluded.

6 ACTIVITY

Neuroprotective; Cerebroprotective; Immunosuppressive; Anticonvulsant; Antinociceptive; Antidepressant; Nootropic; Antiparkinsonian; Virucide; Antibacterial; Tranquilizer; Neuroleptic; Antidiabetic; Antiemetic; Analgesic; Antiaddictive; Analgesic.

7 MECHANISM OF ACTION

Metabotropic Glutamate Receptor-1 (mGluR1 receptor) Antagonist.

In receptor binding assays using CHO cells expressing the mGluR1 receptor, 3-ethyl-6-(IH-tetrazol-5-yl)-1,2,3,4-tetrahydro-9H-thioxanthen-9-one (Ia) had an IC₅₀ of 9 nM.

8 USE

(I) are used as medicaments (claimed), useful for the treatment and/or prophylaxis of neuronal damage diseases or diseases associated with disorders of the glutamatergic system in the central and peripheral nervous system, specifically: (i) neuronal damage associated with ischemic, thrombotic, thrombo-embolic or hemorrhagic stroke, direct or indirect cerebral-cranial injury or post-operative cerebral ischemia; (ii) primary or secondary cerebral

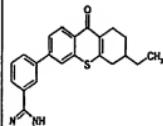
| DE 10126434-A+/1

2003-211999/21

disorders, e.g. associated with cerebral vasospasm, hypoxia/anoxia, preinatal asphyxia, autoimmune, metabolic or organ diseases, convulsions, atherosclerosis or arteriosclerosis; (iii) chronic or psychiatric diseases such as depression, neurodegenerative diseases (e.g. Alzheimer's disease, Parkinson's disease or Huntington's disease, multiple sclerosis, amyotrophic lateral sclerosis, neurodegeneration due to viral or bacterial infections or multi-infarct dementia; (iv) dementia of various origins, cerebral insufficiency in the elderly, memory disorders, bone marrow injury, anxiety states, drug-induced Parkinsonian syndrome, psychosis (e.g. schizophrenia), cerebral edema, neuronal damage after hypoglycemia, emesis, nausea, obesity, substance abuse and withdrawal symptoms, CNS-mediated spasms, sedation or movement disorders; or (v) acute and/or chronic pain, especially cancer-induced pain or chronic neuropathic pain. (I) are especially used for the treatment and/or prophylaxis of pain or neurodegenerative diseases (claimed).

9 SPECIFIC COMPOUNDS

165 Compounds (I) are disclosed, e.g. 3-ethyl-6-(IH-tetrazol-5-yl)-1,2,3,4-tetrahydro-9H-thioxanthen-9-one (Ia).



(Ia)

10 ADMINISTRATION

Dosage is 0.001-10 mg/kg, preferably 0.005-3 mg/kg in the case of oral administration. (I) are preferably administered orally, parenterally or transdermally, although inhalative or topical administration is also possible.

11 EXAMPLE

A mixture of 0.5 g 3-ethyl-9-oxo-2,3,4,9-tetrahydro-1H-thioxanthene-6-carbonitrile, 0.51 g triethylammonium hydrochloride

| DE 10126434-A+/2

and 0.24 g sodium azide was stirred in toluene overnight at 100 °C, cooled, stirred with water and toluene, acidified to pH 3 with hydrochloric acid and further stirred. The obtained solid was filtered off, washed with water, dried and recrystallized from cyclohexane/ethyl acetate to give 3-ethyl-6-(1H-tetrazol-5-yl)-1,2,3,4-tetrahydro-9H-xanthen-9-one (I; 290 mg; 50%).

DEFINITIONS

Preferred Definitions:

R₁ = (i) phenyl or 5- or 6-membered heteroaryl (both os by 1 or 2 of halo, CN or 1-3C alkyl); or (ii) 5-7 membered heterocycl (os by one or more of 1-3C alkyl or oxo);

A = direct bond, NR₂, SO₂NR₂ or NR₂CO;

R₄, R₅, R₆ = optionally unsaturated 1-3C alkyl (os by 1 or 2 of OH or OMe) or H;

R₂ = H;

D = (CH₂)_m-CR₁₆R₁₇-(CH₂)_n (having a total of 3-6C);

m, n = 0-2;

R₁₆, R₁₇ = H or 1-3C alkyl;

CR₁₆R₁₇ = 3-6C cycloalkylidene;

The -R₁A- group is in the 3-position.

TECHNOLOGY FOCUS

Organic Chemistry - Preparation: (I) are generally prepared by introducing and/or modifying the group -AR₁. Typically a corresponding halo compound having -AR₁ replaced by Br or Cl is reacted with:

(i) a boron compound of formula R₁₉-BR₂₀R₂₁ (III) in a solvent in presence of a catalyst (preferably under Suzuki coupling conditions) to give (I; -AR₁ = R₁₉);

(ii) a heterocyclic compound of formula R₂₂-H (IV) in a solvent to give (I; -AR₁ = R₂₂); or

(iii) an active hydrogen compound of formula R₁-G-H (V) in a solvent in presence of a catalyst to give (I; A = G).

R₁₉ = as for R₁ (i);

R₂₀, R₂₁ = OH;

BR₂₀R₂₁ = 3,3,4,4-tetramethyl-1-bora-2,5-dioxacyclopentane;

R₂₂ = N-bonded 4-12 membered heterocycl (os as in R₁ (ii));

G = O, S or NR₂.

(88pp2400DwgNo.0/0)

DE 10126434-A/3

BEST AVAILABLE COPY